

A Meta-analysis to Investigate the Relation Between Fitzpatrick Skin Types and Tolerability of Adapalene-Benzoyl Peroxide Topical Gel in Subjects with Mild or Moderate Acne

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ABSTRACT

The overall goal of acne management for all patients is to select treatments that effectively address as many pathogenic factors as possible while minimizing side effects. Acne therapy in darker skin patients presents unique challenges due to differences in the risk of postinflammatory hyperpigmentation, which may develop in response to acne itself or to irritation secondary to treatment. One combination treatment currently available is a gel formulation containing a retinoid (adapalene 0.1%) in fixed combination with an antimicrobial (benzoyl peroxide 2.5%). Results from three randomized, double-blind, vehicle-controlled, clinical trials of adapalene-benzoyl peroxide were combined in a retrospective meta-analysis that included 909 patients treated for 12 weeks and assessed at each visit for erythema, scaling, dryness, and stinging/burning. Only Week 1 results were included in the meta-analysis because the worst severity of cutaneous irritation was found to occur at this timepoint in all three trials. For each study, and for the meta-analysis, comparisons were made using the Cochran-Mantel-Haenszel test. There were no statistically significant differences in dryness, scaling, and stinging/burning with adapalene-benzoyl peroxide treatment when subjects with Fitzpatrick skin types I to III were compared to subjects with Fitzpatrick skin types IV to VI ($P=NS$). Erythema assessments were statistically different based on skin types, as subjects with Fitzpatrick skin types IV to VI were rated as having “none” more often than those with Fitzpatrick skin types I to III ($P<0.001$). This could be due to the difficulty in visualizing erythema in patients with darker skin types, mainly Fitzpatrick skin types VI. Acne patients with Fitzpatrick skin types IV to VI were not found to be more susceptible to cutaneous irritation from treatment with the adapalene-benzoyl peroxide gel than patients with Fitzpatrick skin types I to III. (*J Clin Aesthetic Dermatol.* 2010;3(8):15–19.)

Acne affects individuals of all races and ethnicities. The pathogenesis of acne is multifactorial, and the same factors are probably involved across the spectrum of skin types: sebaceous follicle obstruction, excessive sebum production due to hormonal stimulation of sebaceous glands, and proliferation of *Propionibacterium acnes*, which produces chemotactic factors and proinflammatory mediators that, in turn, generate an inflammatory response, followed by follicular rupture and extension of inflammation into the

dermis, resulting in the formation of inflammatory lesions.^{1,2}

The overall goal of acne management in all patients is to select treatment that effectively addresses as many of the pathogenic factors as possible while minimizing side effects.^{3,4} Using multiple agents at the same time during treatment (concomitant therapy) has been recommended as a rational means to achieve this goal.^{5,6} Acne therapy in skin of color (high melanin content) presents unique challenges due to differences relating to acne sequelae in

DISCLOSURE: Dr. Callender is a clinical researcher and consultant for Galderma. Drs. Preston, Osborn, Johnson, and Gottschalk are employed by Galderma.

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TABLE 1. Demographic characteristics and baseline disease severities of patients enrolled in the adapalene-BPO arm in each of the three studies

BASELINE CHARACTERISTICS	ALL STUDIES (N=909)
Age	(Years)
Mean	18.6
Minimum, maximum	12, 58
Gender	(%)
Male	49%
Female	51%
Race	n (%)
Caucasian	664 (73%)
Black	104 (11%)
Hispanic	103(11%)
Other	38 (4%)
Phototype	n (%)
I–III	569 (63%)
IV–VI	340 (37%)

BPO=benzoyl peroxide

these skin types, especially the presence or risk of postinflammatory hyperpigmentation (PIH) and keloidal scarring,^{7–10} which are more prevalent in darker skin.^{11–13}

Current acne treatment recommendations include combining gentle cleansing, effective moisturization, and sun protection, along with lower concentrations of benzoyl peroxide (BPO, 2.5%, 5%) and topical retinoids (adapalene 0.1%, tretinoin microsphere 0.04%, tazarotene 0.05%).^{6,7,14} These agents can then be titrated up to higher concentrations if tolerated by the patient. Recently, a fixed-dose combination product containing a retinoid (adapalene) in combination with an antimicrobial (BPO) became available. Retinoids, such as adapalene, tretinoin, and tazarotene, are ideally suited for acne therapy because they target key factors in hyperkeratinization and comedogenesis, and are anti-inflammatory.¹⁵ Adapalene itself possesses anticomedogenic, comedolytic, and anti-inflammatory properties.^{16–19} Some studies have documented that retinoids in skin of color, in addition to effectively treating noninflammatory and inflammatory acne, may also improve PIH.^{20–23} Antimicrobials, such as BPO, provide additional benefits. BPO is an oxidizing agent with antibacterial and keratolytic effects and is used in acne treatment for its activities in decreasing the bacterial population of *P. acnes*.^{24–27} In addition, the nonclinical and clinical safety profile of BPO is well established.²⁸

Despite the benefits of combination therapy, the potential for increased cutaneous irritation is a concern. Although it has not been established that skin of color is more or less

sensitive to irritants,²⁹ PIH may be triggered in darker skinned patients by skin irritation independent of cause (i.e., a disease or iatrogenic cause).^{11,21,30} This issue has led some physicians to believe that skin of color is more sensitive to irritation from therapy. Because acne-related PIH is caused by a response to skin inflammation,^{7,8} minimizing inflammation and reducing potential irritation and dryness is also a key goal in treating acne in skin of color. This is why dermatologists who treat acne patients with darker skin strive for a balance between effectively treating acne lesions and recognizing the importance of tolerability.

This meta-analysis of the cutaneous irritation of adapalene-BPO gel was conducted to investigate possible differences in the incidence and severity of irritation among patients with different skin types. Three randomized, double-blind, vehicle- and placebo-controlled, clinical trials involving 3,855 patients have established the safety and efficacy of adapalene-BPO gel in the treatment of acne for all skin types.^{31–33} The present retrospective meta-analysis is based on the tolerability data from those patients who were assigned to the adapalene 0.1%–BPO 2.5% treatment arm in each of the three randomized trials.

METHODS

All three studies had similar objectives and design. They were multicenter, randomized, double-blind, parallel-group, active- and vehicle-controlled studies. Study 1 was conducted at 60 centers in the United States, Puerto Rico, and Canada. Study 2 was conducted at 61 centers in the United States, Canada, and Europe, and Study 3 was conducted at 36 centers in the United States. The efficacy and safety of the adapalene 0.1%–BPO 2.5% combination gel (Epiduo®, Galderma Laboratories, LP) was compared with adapalene and BPO monotherapies as well as the gel vehicle. Participants were randomized to adapalene-BPO combination gel, adapalene gel monotherapy, BPO gel monotherapy, or gel vehicle. Efficacy and safety evaluations were performed at baseline and Weeks 1, 2, 4, 8, and 12 and included investigator ratings of erythema, scaling, dryness, and stinging/burning on a scale ranging from 0 (none) to 3 (severe).

Patients enrolled in the three studies were male or female of any race, 12 years of age or older with facial lesions counts (excluding the nose) between 20 and 50 for inflammatory lesions and between 30 and 100 for noninflammatory lesions, no cysts and no more than one nodule in Studies 1 and 2 (no cysts or nodules in Study 3).

All studies included in this meta-analysis were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and Good Clinical Practices and in compliance with local regulatory requirements. The studies were reviewed and approved by an institutional review board or ethics committee. Prior to the performance of any study procedures, written informed consent was obtained from all participants.

This meta-analysis included subjects who were randomized to the adapalene-BPO treatment group in each of the three studies. In all three studies, it was determined

TABLE 2. Cutaneous reactions severity at Week 1 in patients enrolled in the three studies, stratified by Fitzpatrick skin type

	FITZPATRICK SKIN TYPES I–III				FITZPATRICK SKIN TYPES IV–VI				<i>p</i> -value ^a
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	
Study 1 ^b	N=225				n=154				
Erythema	100 (44%)	95 (42%)	27 (12%)	3 (1%)	105 (68%)	36 (23%)	12 (8%)	1 (1%)	<0.001
Scaling	143 (64%)	70 (31%)	11 (5%)	1 (0%)	107 (69%)	38 (25%)	9 (6%)	0 (0%)	0.278
Dryness	126 (56%)	83 (37%)	15 (7%)	1 (0%)	93 (60%)	48 (31%)	13 (8%)	0 (0%)	0.505
Stinging/ burning	122 (54%)	74 (33%)	23 (10%)	6 (3%)	80 (52%)	51 (33%)	20 (13%)	3 (2%)	0.611
Study 2 ^c	N=256				n=137				
Erythema	115 (45%)	98 (38%)	41 (16%)	2 (1%)	68 (50%)	47 (34%)	22 (16%)	0 (0%)	0.428
Scaling	149 (58%)	87 (34%)	17 (7%)	3 (1%)	76 (55%)	44 (32%)	15 (11%)	2 (1%)	0.413
Dryness	109 (43%)	115 (45%)	26 (10%)	6 (2%)	64 (47%)	56 (41%)	14 (10%)	3 (2%)	0.508
Stinging/ burning	119 (46%)	85 (33%)	35 (14%)	17 (7%)	63 (46%)	46 (34%)	20 (15%)	8 (6%)	0.959
Study 3 ^d	n=88				n=49				
Erythema	40 (45%)	36 (41%)	12 (14%)	0 (0%)	27 (55%)	20 (41%)	2 (4%)	0 (0%)	0.146
Scaling	53 (60%)	20 (23%)	15 (17%)	0 (0%)	32 (65%)	16 (33%)	1 (2%)	0 (0%)	0.252
Dryness	40 (45%)	35 (40%)	12 (14%)	1 (1%)	31 (63%)	17 (35%)	1 (2%)	0 (0%)	0.017
Stinging/ burning	48 (55%)	27 (31%)	12 (14%)	1 (1%)	25 (51%)	17 (35%)	6 (12%)	1 (2%)	0.754
All Studies Combined	n=569				n=340				
Erythema	255 (45%)	229 (40%)	80 (14%)	5 (1%)	200 (59%)	103 (30%)	36 (11%)	1 (0%)	<0.001
Scaling	349 (61%)	177 (31%)	43 (8%)	4 (1%)	215 (63%)	98 (29%)	25 (7%)	2 (1%)	0.555
Dryness	275 (48%)	233 (41%)	53 (9%)	8 (1%)	188 (55%)	121 (36%)	28 (8%)	3 (1%)	0.073
Stinging/ burning	289 (51%)	186 (33%)	70 (12%)	24 (4%)	168 (49%)	114 (34%)	46 (14%)	12 (4%)	0.629

^a All *p*-values associated with CMH test applied to severity distributions, controlling for clinical site in individual study analyses, and controlling for clinical site and study number in the combined-study analysis.

^b Study 1: Stein Gold et al, 2009 (Phase 3 in United States, Puerto Rico, and Canada)

^c Study 2: Gollnick et al, 2009 (Phase 3 in United States, Canada, and Europe)

^d Study 3: Thiboutot et al, 2007 (Phase 2/3 in United States)

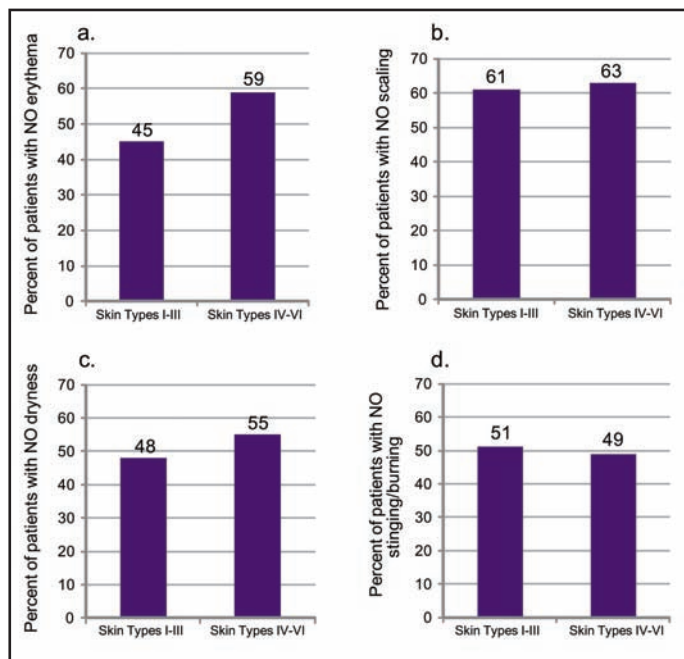


Figure 1. Percent of patients who did not experience any sign/symptom of a) erythema, b) scaling, c) dryness, and d) stinging/ burning at Week 1, stratified by Fitzpatrick skin type (I–III versus IV–VI)

that Week 1 represented the worst severity of irritation, so only Week 1 assessments were included in this meta-analysis. For each study, and for the combined-study meta-analysis, subjects with Fitzpatrick skin types (FST) I to III were compared with subjects with FST IV to VI.

Each tolerability score for erythema, scaling, dryness, and stinging/burning, was treated as a categorical variable. Cochran-Mantel-Haenszel (CMH) tests were used to determine statistically significant differences between subpopulations, controlling for study site in the analysis of individual studies and for study site and study number in the combined-study meta-analysis.

Additionally, a sensitivity analysis was performed using the CMH test to investigate whether combining the three clinical studies had introduced a bias. To investigate differences between the groups of patients treated in each study and in the combined-study analysis, the CMH test controlling for potentially confounding variables was used to test relationships (if any) among the four groups.

All tests were two sided and used the 0.05 level to declare significance. No adjustment for multiplicity was made.

RESULTS

A total of 983 patients received at least one dose of adapalene-BPO in the three studies. The meta-analysis population includes 909 patients, as 74 patients (7.5%) who did not return for Week 1 visit were not included in the analysis. The majority of patients was Caucasian (73%), 11 percent were Black, and 11 percent were Hispanic (Table 1). Sixty-three percent of the patients had FST I to III while 37 percent had FST IV to VI.

There were no statistically significant differences in the

demographics variables among the three studies, thus allowing the studies to be combined into a meta-analysis. When general linear models were used to model the data, with tolerability assessments used as dependent variables and other demographic variables and study number used as independent variables, the coefficients for race and FST were not significant ($P=NS$).

The relationship between each of the four cutaneous irritation scores and FST groups is shown in Table 2 for each individual study and for the combined-study analysis. In each of the four signs/symptoms of irritation, 45 percent of the patients or more did not experience the sign/symptom (Figure 1). Among those patients who experienced irritation, the reports were mostly mild; they occurred early and resolved while still on treatment (not shown).

A statistically significant difference in the distribution of erythema severity among subjects with FST I to III compared to subjects with FST IV to VI was noted in the combined-study analysis ($P<0.001$), with more patients with FST IV to VI reporting a score of “none” for erythema (59% versus 45%) and fewer of them reporting erythema as mild (30% versus 40%). The same statistically significant difference was noted in Study 1 ($P<0.001$) although not in Study 2 or 3.

There were no statistical differences in the distribution of scaling or stinging/burning in any of the three individual studies or in the combined-study meta-analysis when subjects with FST I to III were compared to subjects with FST IV to VI. When dryness was compared between FST I to III and FST IV to VI, a statistical difference was noted only in Study 3 ($P=0.017$) but not in the other studies or in all studies combined, with more severe dryness in the FST I to III group than in the FST IV to VI group.

CONCLUSION

This meta-analysis of three randomized, clinical trials was conducted to investigate if patients with skin of color were more sensitive to irritation from topical acne treatment than Caucasians, and specifically, if the tolerability of adapalene-BPO gel treatment was different in subjects with higher versus lower FST. The results of this meta-analysis for subjects treated with adapalene-BPO showed no statistically significant differences in dryness, scaling, and stinging/burning when subjects with FST I to III were compared to subjects with FST IV to VI ($P=NS$). Only erythema assessments were statistically different based on Fitzpatrick skin types with patients who have FST I to III faring worse than those with FST IV to VI ($P<0.001$). Although this latter finding may be explained in part by the fact that mild-to-moderate erythema would be less visible in subjects with darker skin, the results suggest that the adapalene-BPO formulation is not associated with a higher incidence of any signs or symptoms of irritation in patients with higher FST, mainly FST VI. Reports of cutaneous irritation that did occur were mostly mild and occurred early in treatment and resolved.

Results from the present meta-analysis are consistent with those of an earlier meta-analysis based on clinical trials of the single-agent adapalene gel 0.1%, comparing 45 Black

patients to 609 Caucasian patients. In that meta-analysis, adapalene gel 0.1% demonstrated significantly greater cutaneous tolerability in the subgroup of Black patients, as evidenced by a decreased incidence of erythema and scaling in that subgroup.³⁴

Based on this meta-analysis involving 909 subjects across three clinical trials conducted in the United States, Europe, and Puerto Rico, adapalene-BPO formulation does not appear to be associated with a higher incidence of irritation in patients with darker skin (FST IV–VI) when compared to lighter skin patients (FST I–III).

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